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DOI:
10.1017/S0959259811000037

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Jones, CM 2011, 'Failing to adapt – the ageing immune system's role in cancer pathogenesis', *Reviews in Clincial Gerontology*, vol. 21, no. 03, pp. 209-218. https://doi.org/10.1017/S0959259811000037

Reviews in Clinical Gerontology 2011 21; 209–218 First published online 24 February 2011
 doi:10.1017/S0959259811000037

Failing to adapt – the ageing immune system's role in cancer pathogenesis

Christopher M Jones
School of Clinical & Experimental Medicine, University of Birmingham, UK

Summary

A person's risk of developing cancer rises exponentially with age, an increase that is widely considered to result from cumulative exposure to mutagenic agents. However, cancer incidence rates decelerate and plateau beyond 85 years of age and numerous malignant pathologies peak in incidence during early or middle life, indicating an important role for additional factors in controlling the timing and nature of cancer development. Given that immune function is known to decrease with age, malignant neoplastic change may be induced by increased chronic infection and the onset of a pervasive low grade inflammatory environment. This article discusses in detail the ageing immune system's role in cancer pathogenesis and demonstrates that key polymorphisms coding for relatively low pro-inflammatory cytokine production act to protect some populations from age-induced neoplastic transformation.

Key words: ageing, cancer, immunosenescence, inflammation, neoplasms.

Introduction

From age 30, the population of the UK, and indeed the wider western world, experiences an exponential increase in the incidence of malignant neoplastic pathology (discussed herein as cancer).[1–6] In contrast, immunity appears to decline with age and low-level chronic inflammation becomes commonplace.[7,8] Interestingly, however, cancer incidence rates begin to decelerate and plateau at age 85,[5] and rates of diagnosis of a number of cancers peak many years before. Incidence rates of testicular cancer, for example, are greatest between the ages of 25 and 35, falling thereafter, whilst male bowel cancer incidence rates fall throughout the ninth decade of life.[1–4] These exceptions to the rule, coupled with the relatively low rates of cancer presentation amongst centenarians,[9] provide evidence to suggest that increased exposure to mutagenic agents does not reasonably explain cancer incidence rates in all cases.

It is perhaps confusing then that cancer is frequently discussed as resulting from an accumulation of genetic change as a means of explaining the rise in incidence of this disease with increasing age.[10] Whilst this article will not contest this long-established viewpoint, it will argue that the plateau of cancer incidence rates starting from 85 years of age, coupled with low cancer prevalence in centenarians, indicates that another factor – the immune system – must play a role in age-related cancer pathogenesis. It will further be argued that polymorphisms in genes controlling cytokine production within a set few population groups provide a crucial evolutionary advantage and evidence of adaptation to longer life that is significantly beyond that of the general population.

The role of the extracellular environment in cancer pathogenesis

Cancer is noted most predominantly as a devastating condition of ageing, with increasing age allowing for further exposure to mutagenic insults.[11] In order for a cell to be regarded as cancerous it must commonly possess limitless replicative potential, a lack of response to growth inhibitory signals, an ability to evade apoptosis and a tendency to invade tissues and metastasise. Furthermore, cancer is regarded as a disease of increasing genetic instability, and is thus associated with a multi-step pathogenesis through which no one insult can induce the disease alone.[11] Many cells adopt these changes, although only cancers that form in solid tissues (and not haematological cancers) will be discussed.

Importantly, the genetic makeup of cancerous cells, and their precursors, is influenced by the

Address for correspondence: Christopher Jones, School of Clinical & Experimental Medicine, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT. Email: cmj744@bham.ac.uk

environment in which they reside. Kuperwasser *et al.*[12] have, for instance, elegantly highlighted that seemingly normal epithelial cells from breast tissue can be altered to grow in a malignant fashion under variant extracellular conditions. This, and important work published by Bissell *et al.*[13] in 2003 (which discovered that it was possible to revert malignant breast epithelium back to non-malignant epithelium under differing tissue conditions) have reignited interest in the susceptibility of cancer cells to change induced by their immediate environment.

In their 2004 paper, Schwartsburd *et al.*[14] termed this environment the 'cancer-supportive microenvironment' (CM) or the 'pro-cancer microenvironment' (PCM), depending on the level of instability of the cells in question. The importance of this microenvironment is emphasized further by evidence indicating that cancer cells will only continue to proliferate within a CM,[15] and that some cancer cells actively secrete factors to ensure that their extracellular environment is supportive to their growth.[16] It is consequently appropriate to state that, as part of the multistep pathogenesis model of cancer, mutagenic insults (whether germline or somatic) contribute to the onset of malignant disease but that the age at which such cancers develop and their behaviour upon presentation is ultimately likely to be related to their CM, which is directly under the control of the immune system.

One can thus hypothesize that the ageing immune system, in failing to protect from the pathogenic causative agents of some cancers (resulting in localized inflammation),[7,17] and by aberrantly initiating generalized chronic inflammation,[18] plays a role in modulating the extracellular environment to create a PCM/CM. This, one theorizes, is likely to explain why centenarians often escape cancer despite living longer and why incidence rates for malignant neoplastic pathologies fail to correlate completely with exposure time to potential mutagenic agents.

Immunosenescence

The generalized immune dysfunction seen with increasing age is commonly termed 'immunosenescence' and encompasses a complex array of changes in all aspects of the immune system.[19,20] Many of these changes lead to an increased susceptibility to infection, whilst several more lead to a state of chronic, low-grade inflammation (often termed 'inflammaging'),[17,21–27] although both such forms of immune system change are inexorably linked.[28]

It is likely, particularly in the light of the molecular change accompanying the ageing of an individual, that all cells of the immune system are affected by ageing,[29] although there are many contradictory reports concerning the precise fate of its various components.[8,14,18–21,26–28] Much of this debate centres on the interplay between innate and adaptive immunity, focusing on how changes in the cellular components of the innate immune system are able to influence overall immune function.

The ageing innate immune system

Dendritic cells (DCs), for example, are vital to the immune system's ability to recognize and respond to antigen, but their capacity to migrate to infective sites and phagocytose potential antigen is thought to be impaired in older people.[30] Research attempting to clarify this hypothesis has been relatively unproductive, however, as it remains unclear as to whether this impairment is due to an inherent problem with the DC itself (as suggested by Araki *et al.*,[31] Clague *et al.*[32] and Del Prete *et al.*[33]) or with declining numbers of DCs in old age.[34]

Various research groups have identified potentially raised *in vivo* neutrophil infiltrate in aged individuals when compared with their younger counterparts (Gomez *et al.*[41,42] and Swift *et al.*,[43] amongst others). Yet, apoptosis in these cells during inflammation is reported to occur more readily with increasing age *in vitro*,[44–46] thought to be due to defects in the B-cell lymphoma-2 (Bcl-2) apoptosis regulator protein and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.[45,46] This latter finding, coupled with evidence of poorer phagocytosis and respiratory burst action,[47,48] indicates declining neutrophil function with age partially compensated for by increased bone marrow production.

Eosinophils (acid-staining granulocytes with similar polymorphic nuclei to neutrophils) are vital in the response to parasitic infection but also play a significant role in mediating type 1 hypersensitivity reactions. Asthma is one such reaction and whilst patients with this condition are defined by a

constant eosinophilia throughout life,[49] increased morbidity and mortality in later life indicates declining eosinophil function with increasing age.[50] The eosinophil blood count of healthy individuals has, however, been shown to increase with age (and intriguingly in parallel with IL-6 concentration,[51] raising suggestions of a role for eosinophils in modulating age-related IL-6 levels), supporting the rise seen with neutrophils.

Basophils, and the mast cells these granulocytes give rise to, have failed thus far to demonstrate an overall increase or decrease with age.[29] It is important to note that the significant distribution of mast cells amongst many different tissue types is likely to be responsible for presenting this confusing picture. It is thought, however, that both the number and the effector function of mast cells increases with age; potentially underlying, at least in part, the process of inflammaging.[14]

Macrophages (mononuclear cells derived from monocytes) typically secrete a raft of pro-inflammatory cytokines when activated. *In vitro* evidence appears to indicate decreased cytokine production in some populations of older macrophages.[52–54] This can be regarded as particularly surprising in the context of inflammaging, and *in vivo* evidence points towards an overall increase, rather than decrease, in cytokine production.[55] Exciting new research has, on the other hand, demonstrated decreased tumour necrosis factor-α (TNF-α) production by cutaneous macrophages in older people,[54] supporting the former assertion. The apparent decline in macrophage function with increasing age is supported by findings that indicate decreased phagocytic macrophages in older adults in the face of a potentially increased progenitor number.[56] Macrophages, much like mast cells, reside in multiple different tissues and an examination of their changes with age is confounded as a result.[53] It is thus hypothesized that although their response to acute infection is poorer,[52–54] macrophages in ageing individuals chronically secrete low but pathological levels of cytokines.[53]

More conclusive change is offered by natural killer (NK) and NKT cells, however, with circulating numbers of both cellular populations increasing in older individuals.[55,57] Changes in NK cell number are possibly (though a mechanism is yet to be elucidated) a compensatory response to the age-related decline in the cytotoxic-killing function of these cells.[57] The obvious consequence of such a change is an apparent decrease in the body's ability to fight off viral infection with increasing age, but little research has been conducted with a view to identifying the contribution of NKT cells to immunosenescence.

The ageing adaptive immune system

Many of the changes noted as occurring in the adaptive immune system during ageing are likely to arise as a result of differences in the innate immune system. Of crucial importance is the process of thymic involution that occurs with increasing age. Evidence from mouse models, and more recently *in vivo* human studies, has further enhanced our understanding of this process.[58] Fascinatingly, the thymus is still active in later life (though at a much decreased level to very early life), despite the process of involution potentially starting during early childhood.[59] Unsurprisingly, this decreased activity significantly impacts on T-cell and B-cell lymphopoiesis.

The relative lymphopenia seen in ageing is accentuated by increasingly impaired lymphocyte function overall. One such change, the age-related expansion of antigen-specific CD8+ (and to a lesser extent CD4+) T-cells,[60] is exceptionally well characterized and exceedingly interesting (it may potentially also occur in B-cells, but this is less well characterized).[60] It is thought that this expansion, of T-cells specific for previously encountered antigen, results in a T-cell population primed predominantly for a set few antigenic determinants and unable to rapidly adapt and respond to newly exposed pathogens. Mature naïve T-cells also require 'niche' sites on which they may encounter antigen, but a large population of antigen-specific T-cells is likely to inhibit their ability to reside on these sites and respond to new antigen.[61]

T-regulatory cells (T_{regs}) have also been the subject of much attention from immunologists and gerontologists. Lages *et al.*[62] in 2008 illustrated the more suppressive nature of T_{regs} in older individuals when compared with their younger counterparts, hypothesizing (and supporting with *in vitro* findings) that these cells stifle T-lymphocyte function in older individuals and thus allow for the reactivation of chronic infections. Other studies have supported these findings with evidence of age-related *in vivo* increases in T_{reg} cell number.[54]

Interlinked ageing

The changes discussed thus far have been noted in a very linear fashion but the immune system is exceptionally dynamic, with cells providing constant feedback to one another through secreted factors and direct contact. The result is that no one change occurs without affecting another and that cells of the immune system age as a whole, rather than independently of one another. It is also apparent that contrasting research findings present a confusing picture of the aged immune system. Whilst cancer is the subject of this article, ageing carries further significant consequences. Older individuals suffer from increases in both the number and the severity of acute infections for example, and chronic infections are known to be re-activated as we age.[62] An example of this is the varicella-zoster virus, which re-activates and causes shingles in a significant number of older people. More relevant to cancer, however, are pathogenic agents capable of causing deleterious chronic infection.

Pathogen infection and tumour immunosurveillance

The bacterium *Helicobacter pylori*, and its counterparts human papilloma virus (HPV), hepatitis C virus (HCV) and hepatitis B virus (HBV) amongst many others, have been associated with evading the immune response and causing persistent infection as a result. The outcome of this continual pathogenic presence and the corresponding unrelenting infection is an uncontrolled and undesirable inflammatory response, thought to be largely responsible for the neoplastic transformation induced by these pathogens.[14,40] Whilst this change corresponds well with that induced through the immune system itself in inflammaging, it is exciting to identify how immunosenescence impacts on the immune system's inability to clear harmful bacteria and viruses that may progress to cause malignant neoplastic disease.

It is important to note that a significant proportion of older people may have initially been exposed to a pathogen (that has since unrelentingly infected them) in the early stages of their life. Although the ageing immune system is thus not at fault in terms of the ease at which they are infected, its changing characteristics with age, such as the increase in specific CD4+ and CD8+ T-cells, will affect the potential for carcinogenesis. During ageing, for example, oligoclonal expansion of a T-lymphocyte population specific for the pathogen will lead to a greater inflammatory response against it. Furthermore, pathogen reawakening, occurring as a result of immunosenescence, is likely to cause further damage.

Faced with the presence of *H. pylori*, it is unlikely that the DCs of an aged individual would begin to present antigen and trigger an immune response as effectively as in a younger individual, allowing the bacterium to infect the host. Macrophages in the skin, as has been discussed, would also be limited in their antimicrobial response and research has demonstrated a weakening of their nitric oxide (NO) production.[31] NO release, one of the most effective anti-*H. pylori* responses, is often, but not always, down-regulated by *H. pylori*,[39,40] allowing the bacterium to survive within the host. The reduction in NO production with age is, therefore, likely to uniformly eradicate this effective anti-microbial response. As previously stated, T_{reg} activity also increases with age,[62] and the resultant inhibition of T-lymphocyte helper type 1 (Th_1) activity, for the few (if, indeed, any at all) lymphocytes that may have escaped thymic involution with adequate specificity for epitopes on the surface of *H. pylori*, is likely to result in a further dampened immune response against this pathogen.[62]

A co-ordinated and effective immune response is also vital for the body to effectively eliminate cells recognized to be undergoing malignant change.[63] This 'tumour surveillance' and 'tumour immunity' is likely to be severely dampened in older adults, not least if the antigen receptor pool is diminished in overall sensitivity as a result of oligoclonal expansion. New techniques seeking to utilize the immune system to target cancer cells, as part of the 'tumour immunotherapy' field, are thus likely to need refining and rethinking in the older populations as a result of the decline in the immune system's function. It is important to note, however, that epidemiological evidence indicating a role for the immune system in targeting its own cancer cells has not, as yet, been adequately supported by direct evidence.

The consequences of immunosenescence are severe in terms of allowing pathogenic micro-organisms capable of triggering an inflammatory response to take hold in the body. The decline

in NK cells, though no example is illustrated, is also beneficial to viral agents. Yet this is a paradoxical situation. If the responses of immune cells are dampened with age, how then would such pathogens trigger potentially carcinogenic inflammation? The answer to this question potentially lies in the smouldering, ineffective, cytokine-orchestrated inflammatory state of inflammaging.

Cytokine-driven carcinogenic inflammation

A chronic low-level state of inflammation has been identified in older populations and is associated with the induction of a PCM/CM.[14] This chronic inflammation is thought to stem from low-level persistent infection, chronic exposure to toxic agents or aberrant responses against the body's own antigenic determinants and is co-ordinated by a cascade of cytokine–cellular interactions.[28,64] Although inflammation is thus thought to be deleterious in the state that characterizes inflammaging, when acute it is essentially a protective process, usually occurring in response to pathogenic insult.

Tumour necrosis factor-α and cyclo-oxygenase

Foremost in the pro-inflammatory cytokine hierarchy is TNF-α, which is associated predominantly with the induction of inflammation and neoplastic modulation.[65] This cytokine is typically released from macrophages, though more recent evidence has highlighted a role for T-lymphocytes in its production.[66] It is thought to encourage malignancy through triggering DNA damage and angiogenesis,[65] and by inducing the anti-apoptotic NF-κB transcription pathway.[67,68] The effects of TNF-α are, however, notably pleiotrophic, and very high concentrations of this cytokine are associated with an anti-neoplastic response.[69]

TNF-α is significantly up-regulated during ageing,[70,71] although tissue-specific contradictions are present in the literature. One such discrepancy is the skin; cutaneous macrophages have been noted to synthesize and release decreasing quantities of TNF-α as an individual ages,[54] as previously stated. This would imply a direct role for TNF-α in inducing skin cancer (as it would no longer be found in protective high concentrations) but may also indirectly influence carcinogenesis. This, one theorizes, would occur through reduced cutaneous T-lymphocyte helper type 2 (Th_2) recruitment and a resultant decrease in immunosurveillance; thus allowing pathogens to colonize the skin and cause chronic infection. It is also known that the susceptibility of macrophages to age-related oxidative stress is reduced amongst centenarians,[70] potentially leading to protectively increased TNF-α production amongst this populace.

A study by Bruunsgaard *et al.*[72] assisted in simplifying the controversy surrounding TNF-α levels present in older individuals by inducing infection and identifying the cytokine response. It was found that as age increases, acute TNF-α production is likely to be reduced, whilst more chronic release is greater than that seen in younger individuals. Chronic low-level TNF-α production in the elderly will not only directly increase malignancy but will, intriguingly, interact with COX to indirectly increase malignant potential.[14] These interactions commonly involve chronically raised TNF-α, stimulating the oxidative cytotoxic cascade, thus forming nitric oxide (NO).[73] This NO then interacts with cytotoxic perinitrite ($ONOO^-$) and activates cyclo-oxygenase type 2 (COX-2).[74]

COX-2 produces inflammatory mediator prostaglandins and is thus thought to promote cell proliferation, stimulate angiogenesis and inhibit apoptosis as a result.[75] Interesting epidemiological studies support this hypothesis by indicating that bowel cancer risk (the development of which is closely linked with pervasive inflammation) is decreased amongst patients prescribed NSAIDs (non-steroidal anti-inflammatory drugs; these inhibit the COX enzymes irreversibly or reversibly, depending on the particular formulation).[76]

Of intrigue, therefore, is evidence from the centenarian population that indicates adaptation to lower inflammatory cytokine levels, thus reducing the likelihood of cancer development. COX alleles known to be pro-inflammatory are at much lower incidence amongst this population;[77] for example, the –308A TNF-α SNP single-nucleotide polymorphism (SNP), associated with decreased longevity and increased inflammation when compared with the –308G variant,[78] is at remarkably low incidence amongst both those who live to a greater age and those in low-cancer incidence populations.[77,78]

Highs and lows: interleukin-6 and interleukin-10

Single base changes in the genetic code capable of providing adaptation to a reduced likelihood of cancer development are thus evident. Such genetic modulation appears consistent throughout the many cytokines associated with provoking the chronic, low-grade inflammation seen during ageing. Interleukin-6 (IL-6) is such an example. It is capable of acting both to induce cellular growth and to inhibit apoptosis,[79,80] with several studies even indicating its potential use as a general prognostic factor in cancer.[80] This cytokine has for some time also been associated with the induction of metastases through the up-regulation of endothelial adhesion molecules and by increasing VEGF production.[81,82]

Importantly, the polymorphic –174CG base pair of the IL-6 gene may be changed to provide beneficial adaptation in a select few.[83] If homozygous for the G allele, subjects are known to produce dramatically increased quantities of IL-6 with ageing, increasing cancer incidence amongst these individuals. Centenarians and several population groups with low cancer incidence have, however, been found to feature this allele in exceptionally low incidence whilst polymorphisms providing high quantities of the anti-inflammatory cytokine interleukin-10 (IL-10) are far more prevalent than in the general population.[77] Also of relevance in this context are polymorphic changes controlling eosinophil production, since rising eosinophil number is associated with increased IL-6 concentration in old age.[51]

Interleukin-6 is also known to increase the production of C-reactive protein (CRP),[84] concentrations of which rise during ageing.[85] Intriguingly, CRP is used as a surrogate marker of inflammatory activity,[85] providing evidence of inflammaging, but raised levels have also been associated with the development of bowel cancer,[86] further supporting the link between ageing, inflammation and cancer.

Toll-like receptors

Whilst TNF-α, COX, IL-6 and IL-10 are the principal cytokines to have been strictly associated with ageing, the Toll-like receptor (TLR) family of proteins also appears to be important in age-related cancer pathogenesis.[87] This is likely to be due to their role in 'detecting' the danger signals that fuel the pro-inflammatory cytokine pool. There are many polymorphisms in the TLR genetic code and numerous examples of these are associated with reduced cancer risk, potentially through creating less specific TLRs and thereby reducing the quantity of pro-inflammatory cytokine triggers 'seen' by the immune system.[87,88] This raises the possibility that, whilst certain populaces may be less efficient at eradicating infective micro-organisms, they may be conversely adapted to a longer life free of cancer.

Interleukin-2: paradoxical change?

Concentrations of interleukin-2 (IL-2) are thought to decrease during ageing,[85] which may assist in reducing metastatic spread by limiting angiogenesis (IL-2 is a potent stimulator of VEGF production, indirectly eliciting angiogenesis as a result).[89,90] The decrease in production of this cytokine occurs predominantly as a result of changes in CD4+ T-cells and it is important to note that IL-2 is crucial for foxp3+ T_{reg} peripheral expansion.[62] This appears paradoxical in the light of the age-related increase in T_{reg} activity,[62] and this research conundrum requires further elucidation.

Conclusion

The immune system is complex and dynamic, shifting as a whole to unleash a host of pathological changes in older individuals. Cancer arises principally as a result of an accumulation of genetic change; but the role of the ageing immune system in both the progression and regression of cancers is not to be ignored.

Elegant experiments have demonstrated the ability of the immune system to modulate a cell's malignant potential through modifying its immediate environment. For example, whilst the deteriorating ability of the body to fight off infection with increasing age is likely to assist in the seating of oncogenic micro-organisms within the body, the inflammatory cytokine soup created as a result demonstrates the body's own ability to create a pro-cancer micro-environment. So poor does the immune system's function become with increasing age that tumour surveillance is also severely compromised.

This role for the immune system in controlling cancer pathogenesis is reflected not just by the deceleration and plateau of cancer incidence rates in the very latest stages of life, but by the exceptionally low cancer incidence rates present in some older populations and by the many cancers associated with pathogenic infection and chronic inflammation. Mapping the genetic changes that can adapt the immune system to favour against cancer development in older adults may provide new therapeutic avenues that result in better protection against this complex disease.

Conflicts of interest

The author has no conflicts of interest regarding this article.

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